Allicin as an inhalation therapy in the treatment of Covid-19 infections

Key Messages

- **Laboratory studies have shown allicin, a derivative of garlic, to possess marked antibacterial and antiviral activity**
- **Recent research using a lung model has suggested that allicin can be successfully administered via a nebuliser.**
- **Molecular modelling studies suggest that allicin may inhibit Covid-19 by interacting with the proteases that are a key element of viral replication**
- **Allicin may be a useful adjunct to existing therapies for Covid-19 infections and their sequelae and suggests that a clinical trial be undertaken as a matter of urgency to test this hypothesis.**

Properties of allicin

Allicin, the principal active ingredient in garlic and garlic extracts is a volatile compound with marked antimicrobial and antifungal properties. It is also active against a wide range of viruses including Coronavirus (CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV).

Although generally taken orally, allicin may be administered by the pulmonary route in an aqueous solution *via* a nebuliser, and results of published laboratory studies using a lung model and clinical isolates of pathogenic microorganisms suggest that the extract is likely to be effective for the treatment of pulmonary infections when presented in this way. To date although some anecdotal reports exist which describe the use of nebulised allicin, no controlled clinical trials have been published.

Progression and transmission of Covid-19

The symptoms and severity of COVID-19 vary from asymptomatic disease to severe acute respiratory infection. Fever, dry cough, dyspnoea, myalgia, fatigue, loss of appetite, olfactory and gustatory dysfunctions are the most prevalent general symptoms.

According to Donma *et al*.[1] the condition is characterised by decreased numbers of immune system cells such as suppressed regulatory T cells, cytotoxic and helper T cells, natural killer cells, monocytes/macrophages and increased pro-inflammatory cytokines.

As with most viral infections, the crucial event for the viral life cycle of COVID-19 is the entry of genetic material inside the host cell. This is facilitated by a large number of glycosylated spike (S) proteins which cover the surface of the SARS-CoV-2 virus which bind to the host cell receptor. A type 2 serine protease located on the host cell membrane then promotes virus entry into the cell by activating the S protein. Once in the cell the viral RNA is released

and polyproteins are translated from the RNA genome. Viral RNA is then replicated and structural proteins are synthesized, assembled, and packaged in the host cell after which more new viral particles are released.[2] All of these stages are achieved by the action of different proteolytic enzymes either of the host or the virus acting in a concerted fashion to regulate and coordinate specific steps of the viral replication and assembly. It follows therefore that the proteases involved in these three steps are important potential therapeutic targets because molecules which interfere with their activity could help to prevent virus replication.[3]

Potential mechanisms by which allicin could prevent disease progression

Khubber *et al.*[4] predicted that constituents of garlic could inhibit protease activity by the formation of hydrogen bonds with the protease molecule and Thuy *et al*.[5] used a molecular docking technique to predict the ability of 17 organosulfur compounds found in garlic essential oil to produce an inhibitory effect on the host angiotensin-converting enzyme 2 (ACE2) protein. All the compounds they examined had strong interactions with the amino acids of the ACE2 protein and the main protease of SARS-CoV-2. Similar views on the potential value of allicin and other garlic constituents for the prophylaxis and treatment of COVID-19 infection have been expressed by others.[6-8]

Whilst there is yet no direct evidence that Allicin is active against COVID-19, the ability of garlic extracts to kill many different viruses including Coronavirus (CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) has been reported previously.[9, 10]

Pulmonary infections and the importance of biofilm formation

Patients with Covid-19 can develop acute respiratory distress syndrome resulting in diffuse alveolar damage with inflammatory infiltrates, potentially predisposing to superinfection.[11] Those on ventilators are particularly susceptible and secondary bacterial infections are a significant cause of morbidity and mortality.

Treatment of such infections is complicated by the ability of many bacteria to clump together to form a biofilm within which the cells organize themselves into a coordinated functional community, a process facilitated by the production of a slimy extracellular matrix comprising a polymeric conglomeration of extracellular polysaccharides substances (EPS), proteins, lipids and DNA which forms a protective coating to the cells. A biofilm may contain of a single species or a diverse group of microorganisms and its formation may be initiated by many different factors including exposure of planktonic cells to sub-inhibitory concentrations of antibiotics.

The cells within the biofilm matrix are physiologically distinct from planktonic cells of the same organism and are often resistant to treatment with conventional antibiotic therapy. Biofilms are ubiquitous, forming on living or non-living surfaces including the surface of the lung. *Pseudomas aeruginosa* can cause chronic lung infections, forming biofilm micro-colonies throughout the tissue which are highly tolerant to otherwise lethal doses of antibiotics. The biofilm also protects against the bactericidal activity of polymorphonuclear leukocytes (PMNs).

Effect of allicin on biofilm formation

Biofilm production is influenced by a process termed quorum sensing (QS), by which bacteria interact or 'communicate' with each other by means of small diffusible signalling molecules which pass between cells. These activate the expression of genes which, in addition to biofilm formation, can control functions like bioluminescence and virulence. It follows that quorum sensing inhibitors (QSIs), chemicals which interfere with QS, may offer therapeutic benefits when used alone or in conjunction with antibiotic therapy in the treatment of different pathogens by preventing biofilm formation.[12]

In addition to its well established activity against a broad spectrum of bacteria and fungi, including multi-resistant strains,[13] garlic constituents, including allicin, have been shown in numerous studies to be effective QS inhibitors, active against numerous species both *in vitro* and *in vivo*.

Lihua *et al*.[14] investigated the effects of allicin on *P. aeruginosa* biofilm formation and the production of quorum-sensing controlled virulence factors such as exotoxin A, elastase, pyoverdin and rhamnolipid. They found that allicin inhibited early bacterial adhesion, reduced EPS secretion, and down-regulated the production of virulence factors leading them to conclude that allicin has potential as a therapeutic agent for controlling *P. aeruginosa* biofilm.

Garlic extract was shown to be active against biofilms produced by other bacterial species including *Escherichia coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Serratia marscens* and MRSA. It also exhibited potent activity against systemic and deep tissue infections induced in mice caused by *P. aeruginosa* and MRSA. No adverse haematological or histological changes were seen in these animals.[15]

Importance of the pulmonary route

Because allicin rapidly passes through cell membranes and reacts with circulating glutathione (GSH), there is some debate concerning its ability to develop sufficient concentrations in tissue to exert the desired clinical effect.[16]This conclusion was based in part on the results of clinical research which suggested that although clinical trials on the effect of consuming garlic or garlic oil capsules on cystic fibrosis patients were encouraging, the treatment did not produce statistically significant results significant improvements.[17]

However laboratory studies, including one involving the use of a lung model, showed allicin to be effective in the vapour phase against a range of clinical isolates of different strains of bacteria including. Multi-drug resistant strains (MDRs) of *Streptococcus pneumoniae* were equally as susceptible to allicin as the non-MDR strains.

It is therefore theoretically possible to deliver allicin to the entire inner surface of the lung using an aqueous solution in a nebuliser, with obvious implications for the treatment of Covid-19 and other serious pulmonary infections.

Using nebulised allicin in conjunction with oral antibiotics could provide an effective treatment option for pulmonary disease, as synergistic effects between garlic extracts and beta-lactams (cefazolin, oxacillin, and cefoperazone) and the antifungals amphotericin-B and polymixin-B has already been demonstrated.

The possible toxicity of allicin administered *via* the pulmonary route has been considered previously.[16] Although cytotoxic to lung cells *in vitro*, toxicity is largely eliminated in the presence of glutathione, known to be present in large quantities in alveolar fluid.

Allicin: The need for a clinical trial

Administration of allicin by nebuliser is not a novel concept as it has formed the subject of anecdotal reports in the literature. However the evidence suggests it is an idea worth revisiting in the present pandemic because of the wealth of scientific data now available.

Allicin liquid appears to be safe, relatively cheap and is freely available. At least two liquid preparations are available in the UK, Allimed Liquid (Allicin International) and Allitech (Dulwich Health).

Given the scale of the current pandemic, it is suggested that that a formal clinical trial to assess the value of nebulised allicin be undertaken as a matter of urgency, but for existing patients with serious pulmonary infections associated with SARS-CoV-2 (Covid 19), and for whom no clearly defined effective form of therapy is available, the administration of a short course of nebulised allicin as an adjunctive treatment must be worthy of serious consideration .

References

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